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REVIEW

Research progress on traditional Chinese medicine animal models of post-stroke depression and pathological insights

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Abstract

Post-stroke depression (PSD) is a common psychiatric complication affecting nearly one-third of stroke survivors, leading to increased disability, mortality, and cognitive decline. Traditional Chinese Medicine (TCM) has proven effective in treating PSD through syndrome differentiation, yet existing animal models primarily reflect Western medical concepts and fail to incorporate the TCM principle of "同病异治" (*treating the same disease with different methods*). This paper provides a review of the current methods for constructing animal models of post-stroke depression (PSD) from the perspective of Traditional Chinese Medicine (TCM) syndrome differentiation and proposes multi-dimensional assessment indicators. By integrating TCM theories with modern biomedical techniques, this study offers a comprehensive framework for deepening the understanding of the pathogenesis and therapeutic evaluation of PSD. This approach not only contributes to advancing PSD research but also paves the way for innovative treatment strategies that combine traditional and modern medicine.

KEYWORDS
animal models, integrative medicine, post-stroke depression, traditional Chinese medicine

1 | INTRODUCTION

Post-stroke depression (PSD) is a common and debilitating psychiatric condition affecting approximately one-third of stroke survivors. Its impact on rehabilitation outcomes, quality of life, and mortality rates underscores the urgent need for effective interventions.[1] Despite advances in Western medicine, current PSD therapies are limited in their ability to address the condition's multifaceted pathophysiology, which includes inflammation, oxidative stress, neuroinflammation, neurotrophic deficiencies, and impaired neuroplasticity.[2,3] Additionally, the roles of the immune system, autonomic nervous system, and hypothalamic–pituitary–adrenal (HPA) axis dysfunction have been identified as critical contributors to PSD.[4,5]

From the perspective of Traditional Chinese Medicine (TCM), PSD is understood as a combination of "郁证" (*depression syndrome*) (depression) and "中风" (*stroke*), rooted in "气血失衡"（imbalances of qi and blood) and dysfunction of the "脏腑" (*zang-fu organs*). This conceptualization provides a holistic framework for diagnosis and treatment, emphasizing individualized approaches. However, most current PSD animal models are based on Western medical definitions, overlooking TCM principles such as "同病异治" (*treating the same disease with different methods*).[6] This disconnect presents a significant gap in research, as models that fail to incorporate TCM syndrome differentiation may not fully capture PSD's complex pathogenesis.

Recent studies integrating TCM with modern biomedical approaches have explored novel animal models for PSD, offering insights into disease mechanisms and therapeutic strategies.

However, existing models often lack standardization, and their evaluation criteria remain inconsistent, which limits their applicability in the context of TCM treatment.[7] To address these challenges, this review proposes a comprehensive framework for PSD research, focusing on the construction and evaluation of animal models that align with TCM syndrome differentiation and modern pathological mechanisms. By constructing animal models from the perspective of TCM, this approach not only helps deepen the understanding of the pathogenesis of PSD but also promotes the practical application of integrative treatment strategies, providing effective reference and support for the TCM treatment of PSD.

2 | ETIOLOGICAL ANALYSIS OF POST-STROKE DEPRESSION BASED ON TCM THEORY

Although the term PSD is not explicitly mentioned in classical texts, modern TCM categorizes PSD within the scope of "郁证" (*depression syndrome*) (depression), reflecting the dual pathology of "中风" (*stroke*) (cerebrovascular accident) and "郁证" (*depression syndrome*) (emotional depression). For example, the "《素问·六元正纪大论》" (*Su Wen Liuyuan Zheng Ji Da Lun*) introduces the concept of "五行郁证" (*depression syndromes of the five elements*), which describes that "木郁达之，火郁发之，土郁夺之，金郁泄之，水郁折之" (*wood depression is resolved by dispersing, fire depression by releasing, earth depression by draining, metal depression by alleviating, and water depression by overcoming*).

Furthermore, the text emphasizes that "百病皆生于郁" (*all diseases arise from depression*)[8] and "凡病无不起于郁" (*no disease exists without originating from depression*).[9] These statements demonstrate that TCM has long recognized the pivotal role of emotional depression in the onset of various diseases. Similarly, the term "中风" (stroke) first appears in the "黄帝内经" (*The Yellow Emperor's Canon of Internal Medicine*),[10] which attributes its etiology to external pathogenic factors, emotional disturbances such as anger, individual constitution, and dietary habits. This reflects the TCM view that stroke and depression are interrelated conditions with reciprocal causative interactions, rooted in internal imbalances of "气" (*qi*), "血" (*blood*), and "脏腑功能" (*organ function*).

In modern medicine, PSD is classified as a neuropsychiatric complication of cerebrovascular disorders. However, in the theoretical framework of TCM's theory of "络" (*collaterals*) or collateral disorders, cerebral vessels and brain collaterals are believed to share both structural and functional homology. This offers a distinctive lens for understanding post-stroke pathology within TCM.

For instance, Academician Wang[11] highlighted the critical interplay of "血瘀" (*blood stasis*), "热毒" (*heat toxin*), and "痰毒" (*phlegm toxin*) after a stroke as key pathogenic factors. He proposed that therapeutic strategies aimed at eliminating these "*toxins*" could significantly enhance recovery from cerebrovascular diseases.

Furthermore, Yang et al.[12] identified PSD as a prototypical model of "因病致郁" (*depression induced by illness*). From this perspective, stroke-related dysfunction of the "脏腑" (*zang-fu organs*) leads to impaired circulation of "气" (*qi*), "血" (*blood*), and "津液" (*body fluids*). These disruptions gradually accumulate, giving rise to "郁证" (*depression syndrome*). Over time, the persistent functional impairments—particularly involving the "心" (*heart zang*), "肝" (*liver zang*), "脾" (*spleen zang*), and "肾" (*kidneys zang*)-converge into a complex and interwoven pathological mechanism underlying the development of PSD.

Additionally, modern research indicates that patients with PSD present with diverse constitutional types, most commonly including "气虚" (*qi deficiency*), "气滞" (*stagnation of qi*), and "阴虚" (*yin deficiency*).[13] These constitutional types not only shape the underlying pathogenesis of PSD but also influence the disease's location, severity, and prognosis. Consequently, identifying and differentiating these constitutional types holds significant clinical value, providing a theoretical basis for individualized diagnosis and treatment strategies in TCM.

3 | INVESTIGATION OF THE MODELING METHODS AND MOLECULAR MECHANISMS OF ISCHEMIC AND HEMORRHAGIC STROKE COMBINED WITH TCM SYNDROMES

Under the guidance of TCM syndrome differentiation, PSD animal models are typically constructed based on observable behavioral and physiological characteristics of the animals, such as mental state, water intake, locomotor activity, fur condition, and patterns of urination and defecation.[14] Commonly used approaches involve combining stroke modeling techniques (e.g. middle cerebral artery occlusion (MCAO)[15] or intracerebral collagenase injection) with multiple interventions to simulate disease-syndrome models that correspond to TCM syndromes. Representative models include "肾虚肝郁" (*kidney deficiency with liver depression*), "气虚血瘀" (*qi deficiency with blood stasis*), "痰瘀互结" (*phlegm and blood stasis interlocking*), "火毒证" (*fire toxin syndrome*), and "肾阳虚证" (*kidney yang deficiency syndrome*).

There is a certain degree of correspondence between modern modeling methods and TCM pathophysiological concepts. For instance, focal cerebral ischemia induced by MCAO reflects the TCM notion of "血瘀" (*blood stasis*),[16] while hemorrhagic injury induced by collagenase injection corresponds to the theory of "离经之血为瘀" (*extravasated blood becoming stasis*).[17] Additional interventions such as high-fat diets, forced swimming, and fasting are employed to mimic the TCM mechanisms of "劳则气耗" (*over-strain consuming essence*), "饮食自倍，肠胃乃伤" (*spleen injury from improper diet*), and "饮食劳倦即伤脾" (*phlegm formation due to dampness*), resulting in "气虚" (*qi deficiency*) and "血瘀" (*blood stasis*) or *phlegm-blood stasis interlocking syndromes*.[18,19] Emotional disturbances induced via the chronic unpredictable mild stress (CUMS) model simulate the "气滞" (*qi stagnation*) mechanism described in "《灵枢 本神》" (*Lingshu·Ben Shen*): "愁忧者，气闭塞而不行" (Worry and sorrow cause the qi to stagnate).[20,21] "肾阳虚" (*kidney yang deficiency*) is modeled through cold exposure, cold diets, or hydrocortisone injection, based on "《素问 至真要大论》" (*Suwen·Zhi Zhen Yao Da Lun*): "诸寒收引，皆属于肾" (*all*

cold-induced contractions pertain to the kidney).[22,23] Administration of hot herbs like *Aconitum carmichaelii* or hypertonic saline replicates "阳盛则热" (*excessive yang transforming into fire*), thereby modeling syndromes related to yang excess.[24–26]

3.1 | Ischemic stroke

The ischemic stroke model integrated with TCM syndrome differentiation is commonly established using MCAO, combined with various interventions such as high-fat diet feeding, intraperitoneal injection of carrageenan solution, forced swimming, or fasting. MCAO induces transient focal cerebral ischemia, leading to increased blood–brain barrier (BBB) permeability,[27] activation of inflammatory and oxidative stress pathways, and ultimately causing neuronal injury.

This model reliably reproduces core pathological features of human ischemic stroke, including the formation of an ischemic penumbra and the development of substantial infarct volumes.[28,29] Moreover, it offers high reproducibility and controllable reperfusion durations, making it a widely accepted tool for investigating neuroprotective mechanisms.

When integrated with TCM principles, these interventions are selected to simulate specific syndromes, such as "气虚" (*qi deficiency*), "血瘀" (*blood stasis*), or "痰瘀互结" (*phlegm-damp obstruction*), based on classical theories like "劳则气耗" (*over-strain consuming essence*) and "饮食劳倦即伤脾" (*dietary and emotional strain impair the spleen*).[18,19] Such combinations aim to enhance the models relevance to both biomedical pathology and TCM syndrome differentiation.

3.1.1 | Modeling method for PSD with "肾虚肝郁证" (*kidney deficiency and liver qi stagnation syndrome*)

In TCM, PSD is classified as a combination of "郁证" (*depression syndrome*) and "中风" (*stroke*), with its occurrence closely linked to liver and kidney dysfunction. Clinically, this syndrome corresponds to symptoms such as emotional instability, cognitive decline, and, in severe cases, dementia-like presentations. To replicate this TCM syndrome in animal models, Chen et al.[30] established a rat model of PSD characterized by *kidney deficiency and liver qi stagnation*, utilizing the middle cerebral artery occlusion (MCAO) method combined with chronic restraint stress (CRS) and social isolation. Similarly, Zhi et al.[31] adopted a comparable modeling protocol and observed typical signs in rats, including dull fur, hypoactivity, weight loss, anhedonia, and general lethargy. Behavioral assessments, such as the sucrose preference test (SPT), forced swimming test (FST), open field test (OFT), and Y-maze test revealed significant anxiety- and depression-like phenotypes, supporting the models validity for simulating PSD with this specific TCM syndrome type.

Mechanistically, this modeling strategy is believed to trigger aberrant activation of multiple molecular pathways implicated in neuropsychiatric and neuroinflammatory processes, including JAK2/STAT3,[30] RhoA-ROCK,[32] and p38MAPK.[31] These signaling cascades are known to mediate key aspects of stroke pathophysiology, such as inflammation, oxidative stress, apoptosis, neuronal injury, and impaired synaptic plasticity. Consequently, their dysregulation contributes to the neurological dysfunctions observed in PSD, including emotional disturbances and behavioral deficits such as anxiety[31] and depressive-like behaviors.[33]

3.1.2 | Modeling method for PSD with "气虚血瘀证" (qi deficiency and blood stasis syndrome)

The ancient medical text "《医家四要》" (*Four Key Points of Doctor*) states,[33] "气为血之帅，血为气之母，气即病矣，则血不得独行，故亦从而病焉" (*qi is the commander of blood, and blood is the mother of qi. When qi becomes deficient, blood cannot flow freely and thus also becomes pathological*). In stroke patients, the depletion of qi impairs cerebral circulation, leading to stagnation of blood in the brain and contributing to stroke onset and progression.[34] To replicate this TCM syndrome, Li et al.[35] established a model by inducing "气虚" (*qi deficiency*) exhaustive forced swimming and fasting, while implementing MCAO to simulate "血瘀" (*blood stasis*), Similarly, Yang et al.[36] applied a multifactorial strategy-combining exhaustive swimming, sleep deprivation, fasting, high-fat diet, and MCAO —to establish a more comprehensive "气虚血瘀证" (*qi deficiency and blood stasis syndrome*) model.

Typical symptoms observed in these models include signs of both "气虚血瘀" (*qi deficiency and blood stasis*), such as fatigue, lethargy, low responsiveness, hypoactivity,[37] dry and shedding fur, darkened tongue, red eyes, and purplish discoloration of the tail and footpads.[38] Biochemical assessments revealed significant increases in total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels, indicating dysregulated lipid metabolism and systemic blood stasis.

Mechanistically, the combination of physical stressors and ischemia activates the NF-κB/iNOS-COX-2 signaling pathway,[38] promoting inflammation and oxidative stress.[39] Concurrently, suppression of the brain-derived neurotrophic factor (BDNF)-TrkB pathway contributes to impaired synaptic plasticity,[40] neuronal injury, delayed cellular repair, and increased apoptosis.[41] These pathological alterations result in anxiety-like behaviors and cognitive impairments in the model animals, as evidenced by reduced time in the target quadrant during the open field test, prolonged escape latency in the Morris water maze, and decreased accuracy in the Y-maze test.[39]

3.1.3 | Modeling method for PSD with "痰瘀互结证" (*phlegm and blood stasis syndrome*)

In TCM, the combination of phlegm and blood stasis is regarded as a core pathological mechanism in stroke, reflecting the critical role of vascular obstruction and impaired circulation in disease progression. To replicate this pathological state in animals, researchers commonly induce hyperlipidemia by administering a high-fat diet to

simulate phlegm syndrome, while employing MCAO to model blood stasis.

For instance, Zhang et al.[42] and Li et al.[43] successfully established PSD models with phlegm and blood stasis features using this combined approach. The animals exhibited classic signs including reduced activity, dull and greasy fur, limb paralysis, hyperlipidemia, and impaired coagulation—closely mirroring clinical manifestations of PSD with this TCM syndrome.

At the molecular level, the PPARγ/LXRα/ABCG1 signaling axis is essential for cholesterol efflux and reverse transport.[39,40] Disruption of this pathway accelerates atherosclerosis and promotes lipid accumulation. Furthermore, dysregulated cholesterol metabolism activates the NF-κB/MAPK pathway, which initiates a cascade of inflammatory responses.[44] This leads to elevated expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, resulting in chronic inflammation, vascular endothelial damage, and increased stroke susceptibility.

In addition, activation of the mTOR/HIF-1α/VEGF signaling pathway[42,43] exacerbates oxidative stress and abnormal cell proliferation, contributing to lipid peroxidation, reactive oxygen species (ROS) accumulation, mitochondrial dysfunction, and DNA damage, ultimately inducing apoptosis.[45]

In summary, these findings offer valuable insights into the pathological basis of stroke in the context of phlegm and blood stasis syndrome. They also highlight potential molecular targets for intervention.[46] For example, activating PPARγ or inhibiting the mTOR pathway may help mitigate lipid metabolism disorders and systemic inflammation, providing novel therapeutic strategies for PSD associated with "痰瘀互结" (*phlegm and blood stasis*).

3.1.4 | Modeling method for PSD with "火毒证" (*fire toxin syndrome*)

During the Qing Dynasty, Chen described in " 《洞天奥旨》" (*Insight into the Profound Themes of Truth*)[47] that "火未必退而气先失，毒未必化而血先涸" (*the fire may not dissipate, but the qi is already lost; the toxin may not be cleared, but the blood has already dried up*).

This statement encapsulates the pathogenesis of "火毒证" (*fire toxin syndrome*) in TCM, wherein retained pathogenic heat disrupts the equilibrium of qi and blood, ultimately resulting in impaired consciousness and systemic dysfunction. In modern biomedical terms, this syndrome aligns with severe neuroinflammatory and metabolic dysregulation, both of which contribute to cerebral damage and vascular disorders implicated in stroke.

To simulate this syndrome in animal models, researchers often employ intraperitoneal injection of carrageenan, a known inflammatory inducer, in conjunction with MCAO followed by reperfusion. Liu Bo et al.[48] successfully established a fire toxin model using this method, observing hallmark signs such as decreased activity, reduced food intake, dull fur, piloerection, dark purplish coloration of ear vasculature, and swollen limbs. Ma et al.[49] further expanded on this model to investigate the co-occurrence of *fire toxin* and *blood stasis* syndromes, highlighting their potential pathological synergy.

Dong et al.[50] introduced an enhanced protocol by inducing blood stasis through MCAO, while administering subcutaneous yeast suspension to trigger "火毒证" (*fire toxin syndrome*). This approach produced a compound stroke model characterized by severe neuroinflammation, vascular congestion, and thrombotic events.

Mechanistically, carrageenan and yeast extract activated proinflammatory signaling cascades such as NF-κB, ERK1/2, and p38,[51,52] resulting in elevated levels of TNF-α and IL-6 and widespread inflammatory cell infiltration. These responses exacerbated vascular stasis and thrombosis,[53] confirmed by reductions in tail blood flow and pathological changes consistent with Fire Toxin, including lethargy, piloerection, and purplish discoloration of the ears.[54,55]

This model highlights the strong link between "火毒证" (*fire toxin syndrome*) and ischemic stroke pathology, particularly the central roles of inflammation and oxidative stress. Fire toxin not only intensifies localized cerebral injury but also induces systemic inflammation via pathways. multiple signaling pathways, these findings closely mirror inflammation-driven mechanisms in modern stroke pathology and suggest actionable molecular targets for intervention. For instance, inhibition of NF-κB[47] or ERK1/2[53] signaling has been shown to attenuate inflammatory responses and prevent stroke exacerbation.

The integration of this syndrome-based model with targeted pathway analysis provides a deeper understanding of fire toxin syndrome from a TCM perspective, while simultaneously offering translational value for contemporary biomedical research and therapeutic development.

3.1.5 | Modeling method for PSD with "肾阳虚证" (*kidney yang deficiency syndrome*)

In TCM, the kidney is regarded as the root of the body's yang energy. Stroke patients, who are typically elderly, often experience age-related decline in kidney function, resulting in yang deficiency.[56] This deficiency disrupts the circulation of qi and blood, leading to insufficient nourishment of the brain and constituting a key pathological basis of PSD.[57]

Zhang et al.[58] developed a rat model of ischemic stroke with Kidney Yang Deficiency Syndrome by combining MCAO with hydrocortisone injection. Successful modeling was confirmed by classic yang deficiency symptoms, including hypo-responsiveness, reduced locomotor activity, aversion to cold, and preference for warmth. Hydrocortisone not only induced autophagy in microvascular endothelial cells and promoted apoptosis but also impaired angiogenesis, leading to hippocampal neuronal damage and affecting cognitive and memory functions.[59] Moreover, by inhibiting the cAMP/PKA signaling pathway, hydrocortisone reduced the expression of neurotransmitters such as 5-hydroxytryptamine (5-HT), ACh, dopamine (DA), and norepinephrine (NE), resulting in pronounced cognitive deficits and anxiety-like behaviors.[60]

When hydrocortisone treatment was combined with CUMS, depressive- and anxiety-like behaviors were further exacerbated. Rats exhibited characteristic signs of "肾阳虚" (*kidney yang deficiency*), such as dull , lusterless fur and increased urine output, Behavioral assessments including the sucrose preference test (SPT), open field test (OFT), and forced swimming test (FST) revealed significant depression-like phenotypes. Biochemical analyses showed marked reductions in serum 5-HT and NE levels,[61] confirming the stability and reproducibility of the kidney yang deficiency PSD model.[62]

In addition, environmental exposure to cold temperature combined with cold diet has also been used to induce "肾阳虚" (*kidney yang deficiency*) in animal models.[23] Cold stress initially activate the PKA pathway to maintain temperature,[63] but prolonged exposure disrupts the HPA axis, elevating angiotensin 1 (ET-1) levels,[64] which in turn impair coagulation homeostasis. These environmental factors further aggravate Kidney Yang Deficiency and deepen systemic metabolic and circulatory disorders, as evidenced by alterations in WBC, RBC, and PLT levels.[65]

At the molecular level, these studies elucidate the multifaceted role of "肾阳虚" (*kidney yang deficiency*) in PSD pathology Both hydrocortisone and cold stress impair cognitive function through direct neuronal injury and autophagy activation, while also inducing systemic immune metabolic dysregulation via signaling pathway modulation. Targeting pathways such as cAMP/PKA, or restoring neurotransmitter balance, may represent promising strategies for treating PSD associated with *kidney yang deficiency*, addressing both cognitive impairment and emotional disturbances.

3.2 | Hemorrhagic stroke

Similar to ischemic stroke, hemorrhagic stroke models are often established using a combination of collagenase injection and other interventions. Collagenase injection into the brain is one of the commonly used methods for inducing cerebral hemorrhage. Studies have shown that it mainly forms hematomas by damaging microvasculature at the injection site,[66] reducing cell viability around the hematoma, and increasing blood–brain barrier disruption.[67] This process generates ROS, triggers inflammatory responses, and results in neurological deficits.[68]

3.2.1 | Modeling method for PSD with "肝阳化风证" (*hyperactive liver-yang causing syndrome of liver-wind*)

Hemorrhagic stroke is fundamentally related to "肝肾阴虚" (*liver and kidney yin deficiency*), with "肝阳上亢" (*hyperactivity of liver-yang*) and "肝阳化风" (*hyperactive liver-yang causing syndrome of liver-wind*) as secondary features. Yuan et al.[69] established a model of "肝阳化风" (*hyperactive liver-yang causing syndrome of liver-wind*) Syndrome by combining oral administration of Fuzi Decoction, hypertonic saline intake, and collagenase injection into the brain. The model was considered successful when rats exhibited neurological deficits, thirst, reduced food intake, and dull fur.[70] Oral administration of Fuzi Decoction further aggravated irritability, increased water intake, and increased susceptibility to startle, inducing renal arteriole sclerosis, which is consistent with the manifestations of "肝阳上亢" (*hyperactivity of liver-yang syndrome*).[70,71] However, hypertonic saline may inhibit VEGF expression, thereby preventing activation of the Notch signaling pathway and reducing BBB permeability.[72,73]

Li Z et al.[71] compared hypertensive rats with "肝阳上亢证" (*hyperactivity of liver-yang syndrome*) to general hypertensive rats, finding elevated ROS and Akt levels, as well as renal vascular proliferation, in the former. This suggests that ROS may induce oxidative stress via the PI3K/Akt pathway. Additionally, this model showed increased levels of malondialdehyde (MDA), heme oxygenase-1, and oxidized glutathione, along with decreased glutathione, which may be associated with the Nrf2 signaling pathway.[74,75]

Other studies using intraperitoneal dopamine injections established similar models, showing significantly elevated levels of renin and ET-1, with gradual normalization of heart rate and respiration after treatment cessation.[76]

3.2.2 | Modeling method for PSD with "痰热腑实证" (*phlegm-heat internal excess syndrome*)

Sun et al.[77] successfully constructed a hemorrhagic stroke model associated with Phlegm-Heat Internal Excess Syndrome by combining intracerebral collagenase injection with oral administration of rat fecal slurry. Ping[78] further refined the model by applying MCAO in conjunction with a high-fat diet and fecal slurry gavage, which significantly elevated serum total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) in rats.

Successful modeling was indicated by hallmark symptoms of the syndrome, including neurological deficits, polydipsia, irritability, and pharyngeal congestion with sputum.[78] Compared to conventional ischemic stroke models, rats with Phlegm-Heat Internal Excess Syndrome displayed more severe dyslipidemia, vascular pathologies such as atherosclerotic changes, and decreased motilin levels, indicating exacerbated metabolic dysfunction.[79,80]

According to Ping,[78] fecal slurry more accurately represents the "internal excess" component of the syndrome, while a high-fat diet simulates the "phlegm-heat" aspect. Their combination offers a more comprehensive and pathophysiologically relevant model for studying this specific TCM syndrome in the context of stroke.

Mechanistically, gut microbiota play a key role in regulating host immune and metabolic responses.[81] Fecal slurry gavage can activate the AMPK-ULK1-P62 signaling pathway via butyrate, leading to mitophagy induction, Nrf2-mediated antioxidant activity, inhibition of ferroptosis, and attenuation of hepatic injury.[82] This highlights the interconnected roles of metabolic disorders, inflammation, and neural damage in post-stroke pathology.

Overall, this model reveals the complex pathophysiology of Phlegm-Heat Internal Excess Syndrome, suggesting that targeting cholesterol metabolism and gut microecological balance[83] may offer novel therapeutic strategies for hemorrhagic stroke and its related TCM syndromes.

4 | EVALUATION OF PSD MODELS

Behavioral evaluations play a critical role in validating PSD animal models and assessing the therapeutic efficacy of interventions. Given that PSD encompasses both neurological impairment and depressive-like behaviors, comprehensive assessments should include sensory, motor, cognitive, and emotional domains.[84] Integrating multiple behavioral paradigms while minimizing environmental interference enhances the scientific rigor and reliability of PSD model evaluation.

4.1 | Behavioral assessment

Behavioral assessment is essential for verifying model validity and investigating the mechanisms underlying PSD. As PSD represents a combination of stroke and depression syndrome in TCM theory, behavioral tests should concurrently evaluate neurological deficits and affective symptoms.[84,85]

Stroke-induced neurological dysfunction is typically characterized by impairments in motor coordination, sensory processing, learning, and memory, whereas depressive-like behaviors are manifested as anhedonia, reduced locomotor activity, and diminished exploratory behavior.

Commonly used neurological evaluation tools include:

Longa Score.
Bederson Score.
Modified Neurological Severity Score (mNSS).
Foot Fault Test (TFFT).
Modified Grip Traction Test (MGTT).
Standard depression- and anxiety-related behavioral tests include:
Sucrose Preference Test (SPT).
Open Field Test (OFT).
Morris Water Maze (MWM).
Forced Swim Test (FST).
Tail Suspension Test (TST).

These methods enable comprehensive assessment of motor-sensory deficits, cognitive impairments, and emotional states, providing multidimensional insights into PSD pathology. However, due to the co-occurrence of motor impairments in PSD animals, performance in certain cognitive and emotional tests (e.g. MGTT, FST, MWM) may be confounded.[86] Therefore, careful selection and combination of behavioral paradigms is essential, especially when evaluating PSD induced by different pathological mechanisms or syndromes.

For instance, Li et al.[87] assessed the impact of gut microbiota modulation on post-stroke neurological and emotional outcomes using neurological scoring, SPT, and OFT. Lai et al.[74,75] investigated the antidepressant effects of bitter almond extract through SPT and neurological scores. Jiang[88] explored the protective role of oxytocin receptor activation in PSD mice using SPT, OFT, and TST.

Despite the availability of diverse behavioral assays lack of standardization, variability in experimental conditions (e.g. temperature, noise, odor), and observer bias contribute to inconsistent results. Future research should aim to (1) minimize environmental interference, (2) incorporate automated video tracking systems, and (3) apply computer vision-based image recognition technologies to objectively quantify behavioral outcomes and reduce human error, thereby improving reproducibility, accuracy, and inter-laboratory consistency.

4.2 | Physiological and biochemical indicators

In addition to behavioral assessments, physiological and biochemical markers are essential for evaluating the pathological mechanisms and therapeutic responses in PSD models. Key indicators include inflammatory cytokines, oxidative stress markers, neurotrophic factors, and neurotransmitters.

4.2.1 | Inflammatory cytokines (IL-1, IL-6, IL-18, TNF-α)

Pro-inflammatory cytokines such as IL-1, IL-6, IL-18, and tumor necrosis factor-alpha (TNF-α) are critically involved in the development and progression of PSD.[89] Elevated levels of these cytokines contribute to neuroinflammation, which disrupts the hypothalamic–pituitary–adrenal (HPA) axis, alters neurotransmitter homeostasis, impairs neurotrophic signaling, and disturbs gut microbiota balance—all of which play integral roles in PSD pathophysiology.[90,91]

Research has shown that vagus nerve stimulation (VNS) can reduce infarct size and improve neurological outcomes by down-regulating TNF-α and other pro-inflammatory cytokines, thereby suppressing post-stroke inflammatory responses.[92]

Moreover, compounds such as resveratrol have demonstrated therapeutic potential by lowering TNF-α, IL-1β, and IL-6 levels, reducing oxidative stress, and modulating key neurotransmitters such as 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF). These effects collectively alleviate depressive-like behaviors in PSD animal models.[92]

4.2.2 | Oxidative stress indicators (SOD, MDA)

Superoxide dismutase (SOD) and malondialdehyde (MDA) are widely recognized markers of oxidative stress. While SOD reflects the organism's antioxidant defense capacity, MDA indicates the severity of lipid peroxidation and cellular oxidative damage. Imbalances in these markers are frequently observed in PSD and correlate with neuronal degeneration and apoptosis.[93,94]

Pharmacological agents such as scutellarin have been shown to enhance SOD activity and reduce MDA levels, thereby mitigating neuronal injury and improving oxidative resilience in stroke models.[95]

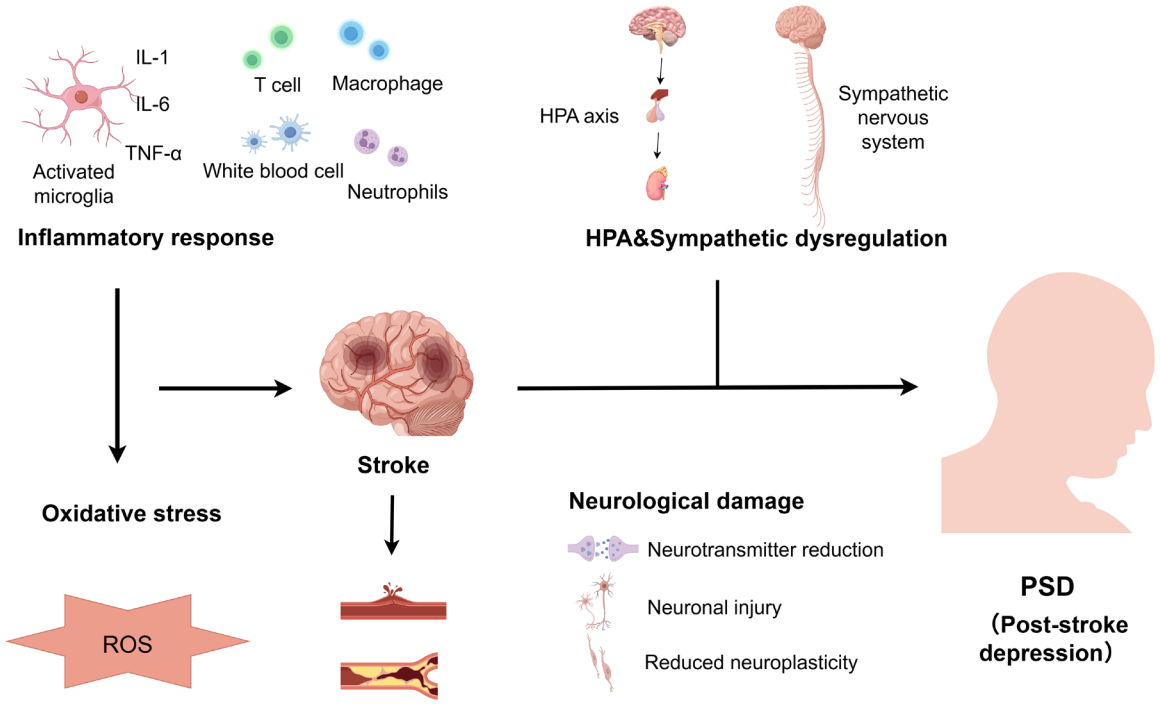

FIGURE 1 This diagram illustrates the key biological pathways involved in the development of PSD following ischemic stroke, highlighting the roles of inflammation, oxidative stress, and dysregulation of the HPA axis and sympathetic nervous system in neuronal injury and neuroplasticity reduction.

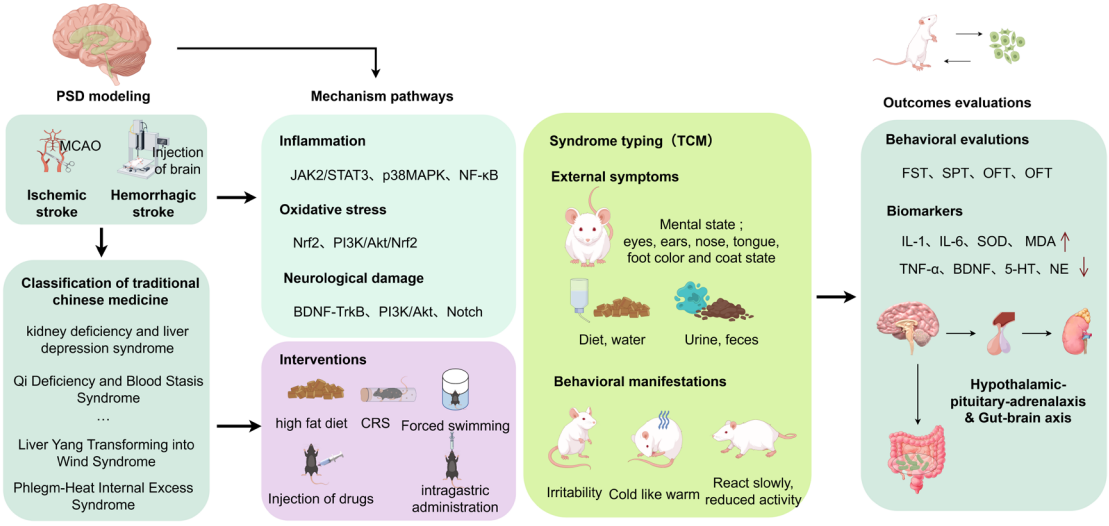

FIGURE 2 Integrated Model of Post-Stroke Depression (PSD) and Its Mechanism Pathways. This diagram outlines the key aspects of PSD modeling, including ischemic and hemorrhagic stroke models, classification of Traditional Chinese Medicine (TCM) syndromes, and the related mechanistic pathways. It illustrates the integration of TCM principles in stroke modeling, including various interventions and syndrome typing based on external symptoms, behavioral manifestations, and biomarkers. The figure also emphasizes the involvement of inflammation, oxidative stress, and neurological damage pathways, as well as the impact on the hypothalamic–pituitary–adrenal (HPA) axis and gut-brain axis.

Likewise, the synthetic triterpenoid CDDO-Im has been reported to decrease both MDA and inflammatory cytokines (e.g. IL-6, IL-1β), resulting in reduced neuronal loss and alleviation of depression-like symptoms in PSD rats.[96]

These findings underscore the importance of modulating oxidative stress pathways as a therapeutic strategy for PSD and its neurological complications.

4.2.3 | Neurotrophic factors (BDNF)

BDNF is a key molecular indicator in PSD, playing a vital role in neuronal survival, synaptic plasticity, and central nervous system recovery.[97] Decreased BDNF levels, especially under chronic stress, are associated with impaired neuroplasticity and are closely linked to the onset and severity of depressive symptoms.[98,99]

TABLE 1 Disease combination model and related pathway analysis of depression.

Disease type	Syndrome type	Research object			Behavioral performance	Biochemical indicators	Pathological histomorphology	Signaling pathway(s)	Refs.
		Animal	Modeling Method	Auxiliary means					
Ischemic stroke	Kidney Deficiency and Liver Qi Stagnation Syndrome	Male SD rats, body weight (300 ± 20) g	Suture embolism (ischemia for 2 h followed by reperfusion, with suture removal after 2 h)	Chronic Restraint Stress (CRS) + Social Isolation	Dull coat, lethargy, and reduced activity		Hippocampal dentate gyrus neural stem cells; hippocampal and cortical neurons	JAK2/STAT3, RhoA-ROCK, p38MAPK	[30–32]
	Qi Deficiency and Blood Stasis Syndrome	Male SD rats, body weight (200 ± 20) g	Suture embolism (permanent occlusion)	Forced Swimming + Fasting Compound Factors (Exhaustive Swimming, Sleep Deprivation, Fasting, High-Fat Diet)	External symptoms: Dry, shedding furPurple tongue, dark red eyesPurplish tail, dark footpads Behavioral manifestations:Fatigue, lethargy, reduced activity Slow response to stimuli	1. PTGS2, SOD, MDA, GSH-Px ; 2. TLR4, IL-1β, IL-6, IL-17, TNF Circulatory and related markers: F2R, cerebral blood flow, CHO, TG, HDL-C, LDL-C, FDP, D-D, VEGF, ATP	Cerebral ischemic area; ATP content	NF-κB/iNOS-COX-2; PI3K/Akt/Nrf2;BDNF–TrkB	[35–37,39]
	Phlegm and Blood Stasis Syndrome	Male SD rats, body weight (200 ± 20) g	Suture embolism (ischemia for 2 h followed by reperfusion)	High-fat diet feeding	Dull coat, limb paralysis, drooping eyelids, purple tongue, slow reactions, and sluggish movement	(1) MPO, SOD, MDA; (2) IL-1α, IL-1β, IL-6, TNF-α, serum NO, VEGF, GSDMD; (3) TC, TG, LDL-C, TBA, AST, ALT (4) Lipid levels, APTT, PT	Infarct area; brain cells; liver cells; abdominal aorta and vascular cell morphology	PPARγ/LXRα/ABCG1; NF-kB/MAPK; mTOR/HIF-1α/VEGF; NLRP3, Caspase-1	[42–44,118–121]
	Fire Toxin Syndrome	Male SD rats, body weight (200 ± 20) g	Suture embolism (ischemia for 1.5 h followed by reperfusion)	Intraperitoneal injection of carrageenan solution	Fluffy fur, dull coloration, reddened ear edges, swollen and red-purple claws, blackened tail	(1) IL-1β, IL-6, TNF-α, MCP-1, IFN-γ (2) PT, FIB, APTT, TT	Brain neurons and ultrastructure, mitochondria; infarct area; brain, spleen, and tail tissues; spleen weight; tail blood perfusion	NF-kB, ERK1/2, p38MAPK	[48–50,53,55,122]
	Kidney Yang Deficiency Syndrome	Male SD rats, body weight (200 ± 20) g	Suture embolism (permanent occlusion)	Intramuscular injection of hydrocortisone injection	Hair loss, polyuria, lethargy, easily startled, hunched posture, cold intolerance with a preference for warmth, reduced appetite, slow reactions, and decreased activity	(1) 5-HT, DA, NE (2) ACh, WBC, RBC, PLT, plasma corticosterone, angiotensin	Nissl bodies in cortical neurons; organ indices of liver, spleen, and kidney	cAMP/PKA	[58,60,61,64,65]

TABLE 1 (Continued)

Disease type	Syndrome type	Research object			Behavioral performance	Biochemical indicators	Pathological histomorphology	Signaling pathway(s)	Refs.
		Animal	Modeling Method	Auxiliary means					
Hemorrhagic stroke	Hyperactive Liver-Yang causing Syndrome of Liver-Wind	Wistar rats, half male and half female, 8–10 weeks old, body weight (200 ± 20) g	Collagenase Injection into the Brain: 0.4 U of Type VII collagenase dissolved in 2 μL of sterile saline (injection site: 1.4 mm posterior to the bregma, 3.2 mm lateral to the right, and 5.6 mm vertically into the brain)	Fuzi Decoction gavage + high-salt water drinking	Increased irritability, fluffy and dull fur, thirst, and reduced food intake	ROS, MDA, HO-1, NQO1, GSSG	Brain tissue water content; peri-hematoma tissue (e.g. inflammatory cells, red blood cells, neurons)	PI3K/ Akt ; Notch ; Nrf2	[69,74]
	Phlegm-Heat Internal Excess Syndrome	Wistar rats, half male and half female, 8–10 weeks old, body weight (200 ± 20) g	Injection of Collagenase VII-Heparin Mixture: 1.25 μL (containing 0.5 U of Collagenase VII and 7 U of Heparin), (injection site: 0.2 mm anterior to the bregma, 4.0 mm lateral to the right of the midline, and 5.5 mm vertically into the brain)	Autologous fecal gavage	Restlessness, increased water intake, increased nasal secretions, phlegm sounds in the throat, dry stools, and increased stool quantity and weight	(1) Oxidative DNA damage, lipid peroxidation, reactive aldehydes (2) Serum TC, TG, LDL-C ; Plasma AST, ALT levels ; Serum motilin, somatostatin levels	Brain index; brain tissue water content	AMPK-ULK1-P62	[77,78,82]

As a result, BDNF is widely regarded as a predictive biomarker for identifying individuals at risk of PSD and as a therapeutic indicator for evaluating treatment efficacy.[100] Pharmacological agents such as antidepressants have been shown to enhance BDNF expression, thereby promoting neural regeneration and mitigating depression-like behaviors.[101]

In addition, TCM formulations such as "柴胡疏肝散" (Chaihu Shugan San) have demonstrated the ability to upregulate BDNF levels in PSD animal models, often accompanied by improvements in emotional regulation and behavioral performance.[102]

Moreover, studies have shown that inhibiting the JAK2/STAT3 signaling pathway can further enhance BDNF expression,[103] offering neuroprotective effects by preventing hippocampal neuronal damage and supporting cognitive recovery.[104,105–107]

Overall, BDNF serves as a central biomarker that reflects both pathological changes and therapeutic responses in PSD, providing a valuable target for future interventions.

4.2.4 | Neurotransmitters (5-HT, NE, DA)

5-HT, NE, and DA are central to the regulation of emotion, motivation, and cognition.[108,109] Decreased levels of these monoamines are strongly associated with the development of PSD. Research has shown that DA and NE pathways TCM formulations (e.g. "解郁汤" (*Jieyu Decoction)*[110]) and acupuncture therapies (e.g. "调神运枢" (*Tiaoshen Yunshu* acupuncture)[111]) have demonstrated efficacy in upregulating 5-HT and NE levels, thereby improving depressive symptoms in both PSD models and patients. Stroke-induced neural damage compromises 5-HT synthesis, storage, and uptake, while pharmacological enhancement of DA signaling has been shown to reverse motor dysfunction and depressive behaviors.[112,113] As such, neurotransmitter levels in brain tissue serve as important biochemical markers for evaluating PSD pathology and treatment efficacy.

4.3 | Histopathological evaluation (infarct size, microglial polarization, synaptic plasticity)

Following stroke, insufficient cerebral perfusion, mitochondrial dysfunction, and neuroinflammation result in extensive neuronal injury or death, leading to the formation of ischemic cores and penumbra zones. These pathological changes activate the brain's innate immune system, particularly microglia, which play dual roles in neuroinflammation and repair.

Among them, M2-polarized microglia are associated with tissue repair, angiogenesis, and synaptic remodeling. Promoting M2 polarization has been shown to reduce infarct volume, attenuate axonal injury, and enhance nerve fiber regeneration.[114]

Synapses, the primary sites for neuronal communication and plasticity, are fundamental to information processing, learning, and memory storage.[115] Microglial polarization profoundly influences synaptic plasticity. Facilitating synaptogenesis and dendritic spine

formation is critical for restoring neural circuit integrity and improving cognitive and emotional outcomes in PSD.[116,117]

Therefore, synaptic plasticity, infarct size, and microglial activation states are important histopathological indicators for evaluating PSD progression and therapeutic efficacy. The mechanism of stroke is shown in Figure 1 and for the cellular mechanisms of PSD, refer to Figure 2. For a summary of stroke disease model modeling methods and other related information, please see Table 1.

5 | CONCLUSION

PSD is a multifactorial disorder involving complex biological and psychosocial mechanisms. Western medicine primarily focuses on neuroinflammation, oxidative stress, mitochondrial dysfunction, and neuronal apoptosis, aiming to elucidate the biological basis of PSD-related neuronal injury. In contrast, TCM emphasizes holistic regulation of organ function and the dynamic balance of *qi*, blood, and body fluids. Despite differing theoretical frameworks, there is considerable overlap in the underlying mechanisms recognized by both systems.

Current TCM-based PSD models are typically developed around classic syndromes such as *kidney deficiency with liver depression*, *qi deficiency with blood stasis*, and *phlegm-heat internal excess*. These models highlight the diversity of pathological processes observed in PSD and reflect TCM's syndrome differentiation approach. However, most models still rely heavily on biomedical techniques, such as MCAO and high-fat diets, and may fail to fully capture the dynamic, individualized, and holistic nature of TCM syndromes. The gap between animal models and clinical syndromic presentations remains a key limitation. observation, listening/smelling, questioning, and palpation.

While modern medical methods can align with TCM mechanisms to some extent, several limitations persist. From the perspective of Traditional Chinese Medicine (TCM), the understanding of PSD involves a holistic approach that includes the regulation of "气" (qi), "血" (blood), and the balance of the "脏腑" (*zang-fu organs*). However, current animal models primarily focus on Western medical definitions and methods, which fail to fully integrate TCM's diagnostic framework, such as its four diagnostic methods "望, 闻, 问, 切" (*observation*, *listening/smelling*, *questioning*, *and palpation*). This gap significantly limits the ability of these models to accurately capture the dynamic nature of TCM syndromes. Furthermore, the differences in disease progression in animal models versus clinical symptoms in humans present additional challenges in replicating the full complexity of TCM syndrome differentiation. Thus, more precise model selection is needed to ensure better alignment with both modern pathophysiology and TCM's holistic understanding of disease mechanisms.

This study summarizes the key TCM syndrome models for PSD and their corresponding mechanisms, offering a framework for future integration of TCM theory with biomedical evidence. A multidimensional, integrative modeling approach will not only deepen our understanding of PSD pathogenesis but also advance the clinical application of TCM in global contexts.

AUTHOR CONTRIBUTIONS

Jielin Wang: Conceptualization; writing – original draft. **Wenlu Ma:** Investigation; project administration; supervision. **Wei Wu:** Software; supervision. **Yujuan Fu:** Funding acquisition; supervision. **Hui Li:** Conceptualization; methodology; supervision; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no financial or non-financial conflicts of interest in this study.

DATA AVAILABILITY STATEMENT

As this is a review article, no new datasets were generated. All data analyzed in this article are available from the cited sources.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As this is a review article, ethics approval and consent to participate are not applicable.

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